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Autism Spectrum Disorders and Coexisting Disorders in a Nationwide Swedish Twin Study

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Abstract

Introduction

Evidence from twin and molecular genetic studies is accumulating that Autism Spectrum Disorder (ASD) shares substantial etiological factors with other disorders. This is mirrored in clinical practice where ASD without coexisting disorders is rare. The present study aims to examine the range of coexisting disorders in ASD in a genetically informative cohort.

Methods

Parents of all Swedish 9-year-old twins born between 1992 and 2001 ($n = 19,130$) underwent a telephone interview designed to screen for child psychiatric disorders, including ASD. To ensure full coverage of child psychiatric disorders, data were also retrieved from population based health registers. We investigated the coexistence of eight psychiatric disorders known to coexist with ASDs in probands and their co-twins.

Results

Half of the individuals with ASDs (50.3%) had four or more coexisting disorders and only 4 % did not have any concomitant disorder. The “healthy co-twin” in ASD discordant monozygotic twin pairs was very often (79% of boys and 50% of girls) affected by at least one non-ASD disorder. The corresponding figures for ASD discordant dizygotic twin pairs were significantly lower (46% of males and 30% of females).

Discussion

Detailed phenotypic descriptions including symptoms of problems associated with a wide range of child psychiatric disorders may aid in unraveling the genetic architecture of ASD and should guide the development of intervention strategies addressing each problem type specifically.

Introduction

Autism Spectrum Disorder (ASD), including the former subgroups Autistic Disorder, Asperger's Disorder and Pervasive Developmental Disorder Not Otherwise Specified, is characterized by deficits in social communication and behavioral flexibility (APA, 2013). Recent epidemiological studies have shown that ASD affects about 1% of the population (Baird et al., 2006). The *direct* causes of ASD remain largely unknown, even when it occurs in the presence of a specific genetic syndrome (Coleman & Gillberg, 2012,). However, twin studies suggest that up to 80% of the variance in ASD may be referred to genetic influences (Folstein & Rutter 1977; Lichtenstein, Carlström, Råstam, Gillberg, & Anckarsäter, 2010).

In addition, accumulating evidence suggests that ASD shares substantial etiology with other developmental disorders. The first twin study of autism (Folstein & Rutter, 1977), reported cognitive difficulties, coordination and language deficits, and/or hyperactivity in 5 out of the 7 monozygotic co-twins considered discordant for ASDs, while only one discordant dizygotic co-twin in 10 displayed a delayed motor milestone and another one a learning disability. A previous report from the twin study used here demonstrated genetic and environmental effects common to ASD and Attention-Deficit/Hyperactivity Disorder (ADHD), Learning Disabilities (LDs), Tic Disorders (TDs), and Developmental Coordination Disorder (DCD) (Lichtenstein, Carlström, Råstam, Gillberg, & Anckarsäter, 2010). Other studies on ASD support the notion of shared etiological factors, Rosenberg et al. (2009), reported data on five coexisting disorders in 277 twin pairs, but only on a group-wise basis, meaning that the degree of overlap between ASD and specific conditions could not be disentangled. Studies of autistic *traits* usually focus on two characteristics, such as in the case of autistic traits and ADHD traits or anxiety traits (Hallett, Ronald, Rijdsdijk, & Happé, 2010 & Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008). Two review articles focusing only on twin studies

(Ronald & Hoekstra 2001; Posthuma & Polderman 2013) are recommended for further reading about the etiological overlap between ASD, autistic traits and other disorders.

In spite of robust behavioral genetic results, molecular studies have shown a far less consistent picture. Candidate gene-based association studies and, lately, genome-wide association studies (GWAS) on ASD have been inconsistently replicated and generally showed small effect sizes (Wang et al., 2009 & Weiss, Arking, Daly, & Chakravarti, 2009). The most important obstacle for successful genetic studies in ASDs has generally been attributed to the heterogeneity of the ASD phenotype. Indeed this notion is supported by studies of rare mutations and Copy Number Variants (CNVs) that have reported associations across ASDs and LDs (Betancur, 2011) and ADHD (Leblond et al., 2012). Furthermore, this has been illustrated in families carrying known rare risk variants (O’Roak et al., 2011; Weiss et al., 2008) where carriers of the same genetic aberration may display different phenotypic characteristics and neurodevelopmental diagnoses. (Stein et al., 2011 & Ballif et al., 2007)

In clinical practice, coexisting disorders in ASD are prevalent (Gillberg & Billstedt., 2000 Simonoff et al., 2008), and have recently come to be regarded as the rule rather than the exception (Gillberg, 2010), and to be crucially important for the design of comprehensive intervention strategies. This has led to the proposal of a new concept - ESSENCE for Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations - linking the vast majority of early onset neurodevelopmental disorders together, highlighting the need for broad and comprehensive clinical examinations (Gillberg, 2010). One of the rationales behind ESSENCE is that most children with neurodevelopmental disorders are impaired in additional areas, not just the one domain that pertains to a particular diagnostic label, and that they therefore require input from several different specialties.

Taken together, accumulating evidence from several avenues of research as well as clinical practice indicate that ASD is far from sharply demarcated either at a genotypic or the phenotypic level. To better understand ASD, to identify their causes and to treat mental health/developmental problems comprehensively, it is essential to understand which other disorders that coexist with ASD and what the coexistence/overlap actually means.

A segment of the current cohort has previously been studied with a view to quantify the statistical effects of shared etiology across ASD, ADHD, LD, TD, and DCD (Lichtenstein, Carlström, Råstam, Gillberg, & Anckarsäter, 2010).. Here, the occurrence of ASDs and coexisting disorders will be presented at the level of the individual so as to better depict the complexity of the ASD phenotype in a way that might be informative to clinicians and researchers alike. After assessing sibling recurrence rates and heritability of ASD in this cohort, we now aimed to (i) characterize, in detail, the ASD-phenotype by simultaneously describing eight different possible coexisting mental and physical disorders in proband twins with ASD and their co-twins, and (ii) compare the rates of these coexisting disorders in ASD-discordant monozygotic vs dizygotic co-twins, in order to illustrate the full range of phenotypical expressions of shared genetic and environmental effects.

Methods

Subjects

All participants were recruited from the ongoing Child and Adolescent Twin Study in Sweden (CATSS), which has been described in detail elsewhere (Anckarsäter et al., 2011). Briefly, since 2002, parents of all twins turning 9 (for some cohorts 12) years in Sweden, are contacted and invited to participate in a telephone interview. Among other measures, the interview includes the Autism-Tics, AD/HD and other Comorbidities inventory (A-TAC

(Hansson et al 2005, Larson et al., 2010 & Larson et al., 2013)). The response rate in CATSS is about 80%, and non-responders differ little from responders with regard to neurodevelopmental disorders (Anckarsäter et al., 2011). In addition, the CATSS has been linked to Swedish population based registries. For the present study, data from the National Patient Register (NPR) was used.

The present report includes twins born between 31st of June 1992 and 1st of January 2001, whose parents have responded for both twins in the CATSS (n=19,130, 51% male). Of those responding, 28.2% were MZ, 35.3% DZ same-sex (ss), 34.3% DZ opposite-sex (os), and 2.2% had unknown zygosity. Zygosity was determined by a panel of 49 single nucleotide polymorphisms. When DNA was not available, an algorithm of questions was used, which was developed based on the parent responses for 571 twins with known zygosity. Only twins with >95% probability of being correctly classified, were assigned zygosity by this method, and 420 twins were therefore excluded on the basis that their zygosity was unknown.

The CATSS study has ethical approval from the Karolinska Institute Ethical Review Board (Dnr 03-672 and 2010/507-31/1), and the linkage to registers has also been approved by the Ethics Committee at Karolinska Institutet (Dnr 2009-939).

Measures

Definition of ASD

ASD was defined in three different ways, (i) through the A-TAC ASD module, (ii) through the NPR, and (iii) by direct questions to parent relating to diagnosis made.

Autism-Tics AD/HD and other Comorbidities inventory (A-TAC)

The A-TAC is a parent telephone interview, organized into modules covering a broad range of neurodevelopmental disorders (Hansson et al., 2005). The A-TAC consists of 96 items that are scored “1” for “yes”, 0.5 for “yes, to some extent”, and “0” for “no”. The A-TAC has been validated both cross-sectionally (Larson et al., 2010) and prospectively in a population-based cohort recalled for later, blinded clinical assessments (Larson et al., 2013). ASD-related symptoms are measured by a 17-item ASD module in the A-TAC, including 12 questions specifically covering the DSM-IV symptom criteria for autistic disorder (299.00). Out of the 17 items, six correspond to the language domain, six to the social interaction domain, and five to the restricted and repetitive behavior domain of the DSM-IV. The ASD score predicts clinical diagnoses of ASDs with an area under the receiver operating characteristics curve of >0.90, which has also been shown in an independent validation by a Spanish group (Cubo et al., 2011). In this paper, the “diagnostic cut-off” of 8.5 was chosen to create proxies for clinical diagnoses of ASD, which yields a sensitivity and specificity of 0.71 and 0.95, respectively, and a population prevalence of 0.9% (Larson et al., 2010).

National Patient Register

At birth, or upon receiving a citizenship, all people living in Sweden are assigned a personal identification number (PIN), which renders linkage across registers possible. The NPR encompasses data on all psychiatric inpatient care since 1987 and includes best-estimate specialist diagnoses assigned according to ICD versions 9 and 10. Since 2001, the register also comprises information from outpatient consultations with specialist physicians. From the NPR, information about a diagnosis of ASD was collected. The validity of the register is continuously evaluated; in individuals with reported ASD, 96.0% (92.0- 98.4) of diagnoses are confirmed when checked against the individual’s medical records (Idring et al., 2012).

Diagnostic questions in CATSS

The CATSS telephone interview also contains specific questions that are worded "has your child ever received a diagnosis of Autistic disorder, Asperger's disorder or Pervasive developmental disorder not-otherwise specified"?

Definition of proband twins with ASD

ASD was defined by (i) scoring at or above high cut-off (>8.5) on the A-TAC, or (ii) a diagnosis of ASDs in the NPR, or (iii) an affirmative answer to the specific questions about a diagnosis of an ASD in the CATSS. In total, 272 individuals with ASD were identified (105, through A-TAC only, 21, through registers only, 47 through self-report only and 99 through combinations of the three). The 47 individuals for whom only the specific question had been endorsed had a mean A-TAC score of 5.5 (CI:s 5.0-6.1, compared to the population mean 0.76, (CI:s 0.74-0.78) and thus corresponded to a "screening diagnosis" of ASDs in the A-TAC validation study (Larson et al., 2010). When excluding those with unknown zygosity ($n=12$), there remained a total of 260 individuals (*proband twins*) with ASD, corresponding to a population prevalence of 1.4% with a male-female ratio of 3.5:1.

Definition of coexisting disorders

Other coexisting disorders were similarly defined through three sources, via the relevant "diagnostic module" on the A-TAC, by the NPR and by open diagnostic questions.

In the A-TAC, screening cutoffs with high sensitivity but lower specificity have been validated for LD, ADHD, TD (Larson et al., 2010) and for Oppositional Defiant Disorder (ODD, Kerekes et al submitted). Obsessive Compulsive Disorder (OCD) has not been included in the validation studies but this module consists of straight-forward questions on the DSM-defined phenomena of obsessions and shows good agreement with clinical practice (Lundström et al., 2013). Finally, a composite of well known neurodevelopmental problems

(motoric, perceptual and executive) were collapsed into one single category, "composite", consisting of the validated modules for DCD and/or executive dysfunctions and/or perceptual problems (Larson et al., 2010). Distributions, Chronbach's α and heritability estimates for all scales can be found in a previous publication (Anckarsäter et al., 2011).

Diagnostic questions in CATSS

In addition to the specific questions about ASD, all parents were asked "does your child have any other disorder that we have not asked about". All written responses to this question have been surveyed by the last author and categorized based, as far as possible, on presumed pathogenesis, for instance chromosomal or brain damage syndromes.

National Patient Register

From the NPR register, information about diagnoses of ASD, ADHD, LD, , TD, ODD, OCD, chromosomal syndromes (ICD-10 Q85, Q90-99) and brain damage syndromes (ICD-10 G00-G39, G45-G46, G80-G94, Q00-Q04) were collected.

ADHD, LD, TD, ODD, OCD and Composite were defined through the A-TAC or the NPR. Chromosomal syndromes and brain damage syndromes were defined via the open questions in the A-TAC or the NPR.

Analyses

Descriptive statistics were calculated on all 19,130 individuals. The 260 ASD proband twins, with known zygosity, were then selected, and coexisting disorders were plotted for both proband twins and co-twins individually, separately for gender and for MZ, DZ-ss and DZ-os twins.. Sibling recurrence rates were defined as the percentage of co-twins meeting criteria for ASD and co-twins meeting criteria for other disorders, but not ASD. Kruskal Wallis and Mann-Whitney U tests were used to test differences in the mean number of coexisting disorders across zygosity.

Heritability estimates

In twin methodology it is possible to disentangle genetic and environmental effects by comparing MZ twins who share 100%, and DZ twins, who share 50% of their segregating alleles. Generally, the genetic and environmental effects are partitioned into standardized variance components: (A) additive genetic effects, (C) shared environmental effects that make the twins more similar, and (E) unique environmental effects that make the twins less similar. Using only MZ and DZ-ss twins (n = 12,140), tetrachoric correlations and liability threshold models were employed to calculate categorical heritability. All analyses were conducted separately for the whole sample and separately for boys and girls. SAS 9.3 and MX were used for all analyses.

Results

Descriptive statistics

The distribution of the screening diagnoses in the entire CATSS (n=19,130) can be seen in **Table 1**. A total of 272 ASDs screen-positive individuals were identified, yielding a population prevalence of 1.4% with a male-female ratio of 3.5:1 (Table 1).

Sibling recurrence rates and heritability estimates

The ASD sibling recurrence rate for MZ was 39% for the full sample (46% for boys and 24% for girls). The corresponding figures for DZ-ss were 8%, 10% and 4% (figure 1 & 2). Univariate heritability estimates based on these figures showed a large genetic component for the collapsed sample: .84 (.50-.95), (82 (.40-.1.0) for boys and .84 (.16-1.0) for girls) (**table 2**). When adding other co-existing disorders, the MZ sibling recurrence rate rose to 89% for boys and 52% for girls, while the corresponding figures for DZ-ss co-twins were 44% and 30%, respectively (**figure 1**).

Coexisting disorders among proband twins with ASD

Eleven of 260 proband twins (4.2%) had no other coexisting disorder identified, yielding a total population prevalence for ASD Only (i.e. ASD without any other disorder) of 5.8 per 10000 (**Table 3, Figure 2**). Half (50.3%) had four or more coexisting disorders. The most frequent coexisting disorders were ADHD (79.3%) and LD (75.0%), followed by TD (36.1%), ODD (36.1%), and OCD (23.8%). Documented brain damage syndromes were present in 7.7% of the proband twins and 2.3% had known chromosomal syndromes associated with ASD, and 74.6% met criteria for 'Composite'.

As expected, the number of coexisting disorders in individuals with ASD did not differ across zygosity: male MZ twins with ASD had an average of 3.3 coexisting disorders, female MZ 3.3, DZ ss male 3.2, DZ-ss female 3.2, DZ-os proband male 3.5 and DZ-os proband female 3.5 (overall $p=.99$).

Coexisting disorders among ASD discordant co-twins

In 32% of the MZ co-twins who were ASD discordant, there was no disorder, while there was one disorder in 68%, and two or more disorders in 52% (**Table 3, Figure 2**) - most commonly ADHD ($n=13/42\%$) and LD ($n=13/42\%$). For 64% of the DZ ASD discordant twins, no disorder was reported.

In the ASD discordant male MZ co-twins, no disorder was reported in 4/19 (21%) (figure 1; figure 2). In discordant male DZ-ss co-twins, 38/63 (54%) had none of the coexisting disorders.

In the female MZ co-twins, no disorder was reported in 6/12 (50%), and 19/27 (70%) of the DZ-ss discordant female twins had no coexisting disorders. For os-twins, where the proband was male 36/53 (68%) had no coexisting disorder while the corresponding figures for os-

twins with female probands were 14/25 (56%). The most common disorders in discordant DZ twins were LD (38/23%) and ADHD (30/18%).

With regard to the average number of disorders there was a significant difference between MZ (1.7) and DZ-ss (0.7) ($p \geq .001$) and MZ and DZ-os (0.7) ($p = .001$). No significant difference was found between male (1.8) and female (1.6) MZ cotwins ($p = .546$). Similarly, no difference was found as regards the number of coexisting disorders across the four DZ groups ($p = .67$).

DISCUSSION

The results presented here demonstrate that ASD without coexisting disorders is extremely rare. The overall rate for coexisting disorders in individuals (twins) with ASD is at least 95%. In addition, MZ co-twins of probands with ASD, who are discordant for ASDs almost always have another type of neurodevelopmental disorder. The findings suggest that (a) molecular genetic research would benefit from broader phenotyping, and (b) compartmentalization into mutually exclusive categories should be avoided in clinical settings. Finally, the visualization of sibling recurrence rates paralleled with heritability estimates may be useful for clinicians and researchers when interpreting results from articles based on twin methodology.

The very considerable variety of neurodevelopmental problems found both in proband twins with ASD and in their ASD-discordant MZ co-twins suggests that a more accurate (broader) phenotype palette is needed in studies aimed at unravelling the biology behind ASD (and other neurodevelopmental disorders) than that covering merely one sharply demarcated clinical diagnosis. This is supported by the results of several other twin studies reporting genetic and environmental overlap between ASD and other neurodevelopmental disorders (Ronald & Hoekstra 2001; Posthuma & Polderman 2013). Among the most interesting

genetic ASD studies in recent years have focused on rare point mutations and submicroscopic variations in chromosomal structure (copy number variations/CNVs), which may be associated with a range of neurodevelopmental problems, not just ASD (Neale et al., 2012 & Pinto et al., 2010). "Mild" diagnostic expressions and general susceptibility for neurodevelopmental problems may be more influenced by common genetic variants, whereas severe forms of ASD with learning disability are more likely to be caused by rare mutations (Geschwind, 2011). In addition, studies of Contactin-Associated Protein-like 2 (CNTNAP2), one of the major candidate genes for ASD phenotypes, show that rare (Bakkaloglu et al., 2008) and common (Stein et al., 2011 & Vernes et al., 2008) variants are associated with ASD of different severity but also hyperactivity and impulsivity (Strauss et al., 2006) as well as TD (Belloso et al., 2007). In this context, by using broad instruments for phenotyping, there might be a better chance that Genome Wide Association Studies/GWAS, mutation screening studies and CNV microarray investigation may present reliable genetic findings and contribute to the understanding of the biology of ASD

The results presented here support the notion of broad multidisciplinary assessments of Early Symptomatic Syndromes Eliciting Neurodevelopmental Examinations/ESSENCE (Gillberg, 2010) that may guide treatment alternatives. In clinical settings, compartmentalization into mutually exclusive categories should be avoided. This may aid in treatment as, for instance, social skills training in ASD is affected negatively by the presence of ADHD (Antshel et al., 2011) and better acquisition of social skills has been noted in children with ASD with a higher level of cognitive function compared to those with lower (Ben-Itzhak & Zachor, 2007). Additionally, the very high sibling recurrence rate for MZ and DZ co-twins suggests that clinicians should always screen for neurodevelopmental problems in co-twins. When researchers discuss discordance and concordance meticulous and careful definitions should be

used. This becomes evident when utilizing the co-twin control design, where the concept of discordance is a key factor.

Strengths and limitations

The main strengths of this study include the high response rate in a nationwide study; use of a validated instrument for assessment, and the additional linkage to national registries, to maximize ascertainment.

However, our findings must be seen in the light of some limitations. Neither the A-TAC, the registries, nor the self-reported questions have perfect sensitivity or specificity, as to why some degree of diagnostic misclassification should be expected. On the other hand, clinical examinations, which would be preferred, are not feasible in a nation-wide study sample. To define co-existing disorders, broad screening diagnoses were used, which inflates the number of coexisting disorders. On the other hand, the screening diagnoses are validated to reflect dysfunction and severity within each diagnostic area (Larson et al., 2010). The sex differences in sibling recurrence rates should be interpreted with caution. ASD in girls may present itself differently (Kopp, Kelly, & Gillberg 2010) and this might also hold true for other neurodevelopmental disorders. Thus, the lower sibling recurrence rate in girls might not adequately reflect the true degree of recurrence. A difference in the mean number of coexisting conditions was found in those who had been picked up as ASD by the A-TAC only (3.97, CIs 3.7-4.2) as compared with those who had a registered diagnosis and endorsed the open question (3.04, CIs 2.5-3.9). This might reflect parental reporting biases but also the severity of ASD, and the findings must therefore be interpreted with caution.

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Table 1. Descriptive data on 19,130 Swedish twins

	Zygoty									
	MZ		DZ-ss		DZ-os		Unknown		Total	
	(52% ♀)		(46% ♀)		(50% ♀)		(45% ♀)			
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	%
ASDs	71	5325	105	6693	84	6486	12	408	272	1.4
Chromosomal syndromes	3	5393	18	6726	22	6548	2	418	45	0.2
Brain Damages	82	5314	96	6648	109	6461	11	409	298	1.6
LDs	791	4593	1071	5664	999	5563	98	321	2959	15.5
ADHD	479	4894	743	5971	668	5880	62	354	1952	10.2
OCD	81	5315	128	6616	100	6470	6	414	315	1.7
TDs	162	5220	221	6505	209	6347	12	406	604	3.2
ODD	138	5258	228	6516	169	5401	18	402	553	2.9
Composite	245	5151	396	6349	354	6216	35	385	1030	5.4

MZ= Monozygotic, DZ-ss = Dizygotic same sex, DZ-os = Dizygotic opposite sex, ASDs = Autism Spectrum Disorders, Chrom = Chromosomal Syndromes, Brain = Brain Damage, LDs = Learning Disabilities, ADHD = Attention Deficit Hyperactivity Disorder, OCD = Obsessive Compulsive Disorder, TDs = Tic Disorders, ODD = Oppositional Defiant Disorder, Composite = developmental coordination disorder and/or executive dysfunctions and/or perceptual problems

Table 2. Tetrachoric correlations, proband-wise concordance rates and heritability estimates.

Correlation (95% CI:s) dichotomous outcome								
All			Boys			Girls		
MZ	DZ		MZ	DZ		MZ	DZ	
.91	.50		.92	.52		.87		.37
(.85-.97)	(.33-.67)		(.86-.99)	(.32-.71)		(.72-.1.0)		(.00-.78)
Proband-wise concordance rates (95% CI:s)								
.56	.15		.63	.18		.40		.07
(.41-.70)	(.07-.27)		(.45-.78)	(.08-.32)		(.14-.69)		(.19-.32)
Estimates of genetic and environmental effects (95% CI:s)								
All			Boys			Girls		
A	C	E	A	C	E	A	C	E
.84	.08	.09	.82	.10	.08	.84	.00	.16
(.50-.95)	(.00-.38)	(.04-.17)	(.45-.1.0)	(.00-.45)	(.03-.16)	(.16-1.0)	(.00-.57)	(.05-1.0)

Note: MZ= Monozygotic, DZ= Dizygotic. A = part of the variance explained by genetic factors, C = part of the variance explained by shared environmental factors, E = part of variance explained by non-shared environmental factors.

Number of coexisting disorders in probands and ASD-discordant co-twins

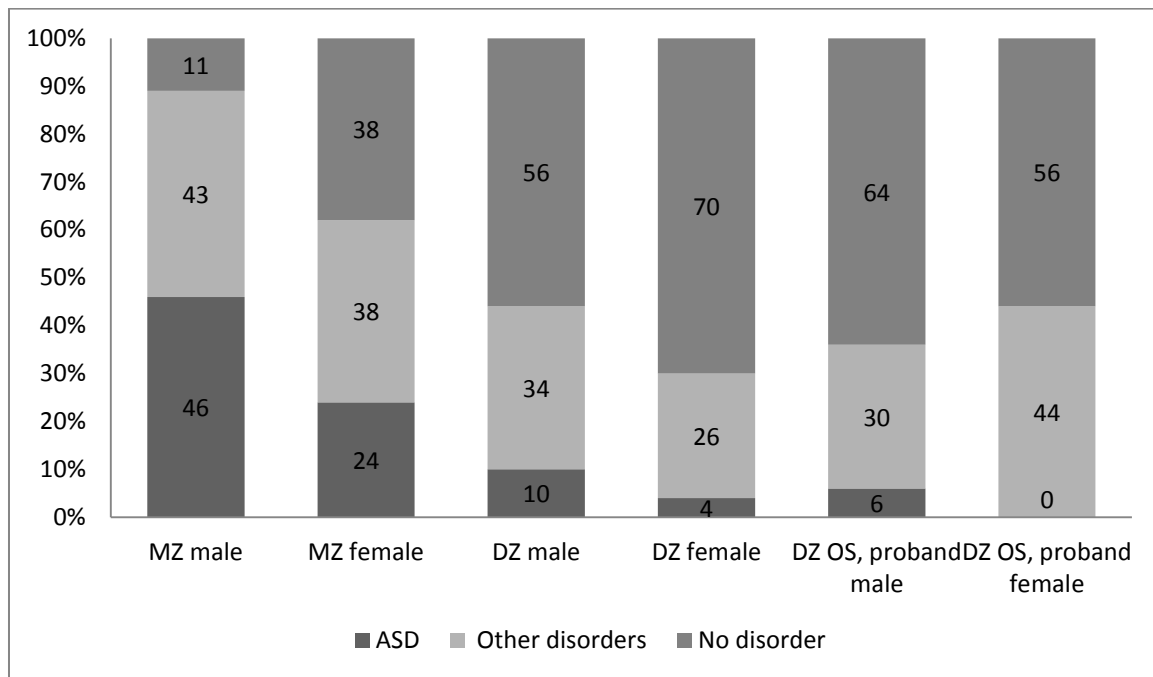
Co-existing disorders	ASD probands		MZ cotwins		DZ-ss cotwins		DZ-os cotwins ^a		DZ-os cotwins ^b	
	n	% [*]	n	% [*]	n	% [*]	n	% [*]	n	% [*]
≥6	14	5.4	0	0	0	-	0	-	0	-
5	40	15,3	1	3,2	1	1,1	1	4,0	2	3,7
4	77	29.6	5	16,1	3	3,4	0	-	0	-
3	58	22.3	4	12,9	5	5,6	1	4,0	2	3,7
2	36	13.8	6	19,4	9	10,1	5	20.0	5	9,4
1	24	9.2	5	16,1	12	13,4	4	16,0	8	15,1
0	11	4.2	10	32,2	57	64,0	14	56,0	36	67,9
Total n	260		31		89		25		53	

Table 3.

Note: *= percentage within the category, ^a= female proband, ^b= male proband

ASD= Autism Spectrum Disorders, MZ= Monozygotic, DZ= Dizygotic, SS= Same sex, os= Opposite Sex.

Figure 1, sibling recurrence rates of ASD and other disorders in probands and cotwins



Note: ■ = percentage of twin pairs where both individuals have ASDs. ■ = percentage of twin pairs where the co-twin display a screening diagnosis of ADHD and/or LD, TDs, OCD, ODD, composite, chromosomal syndromes, and/or brain damage syndromes, but not an ASD. ■ = No ASDs or coexisting disorders

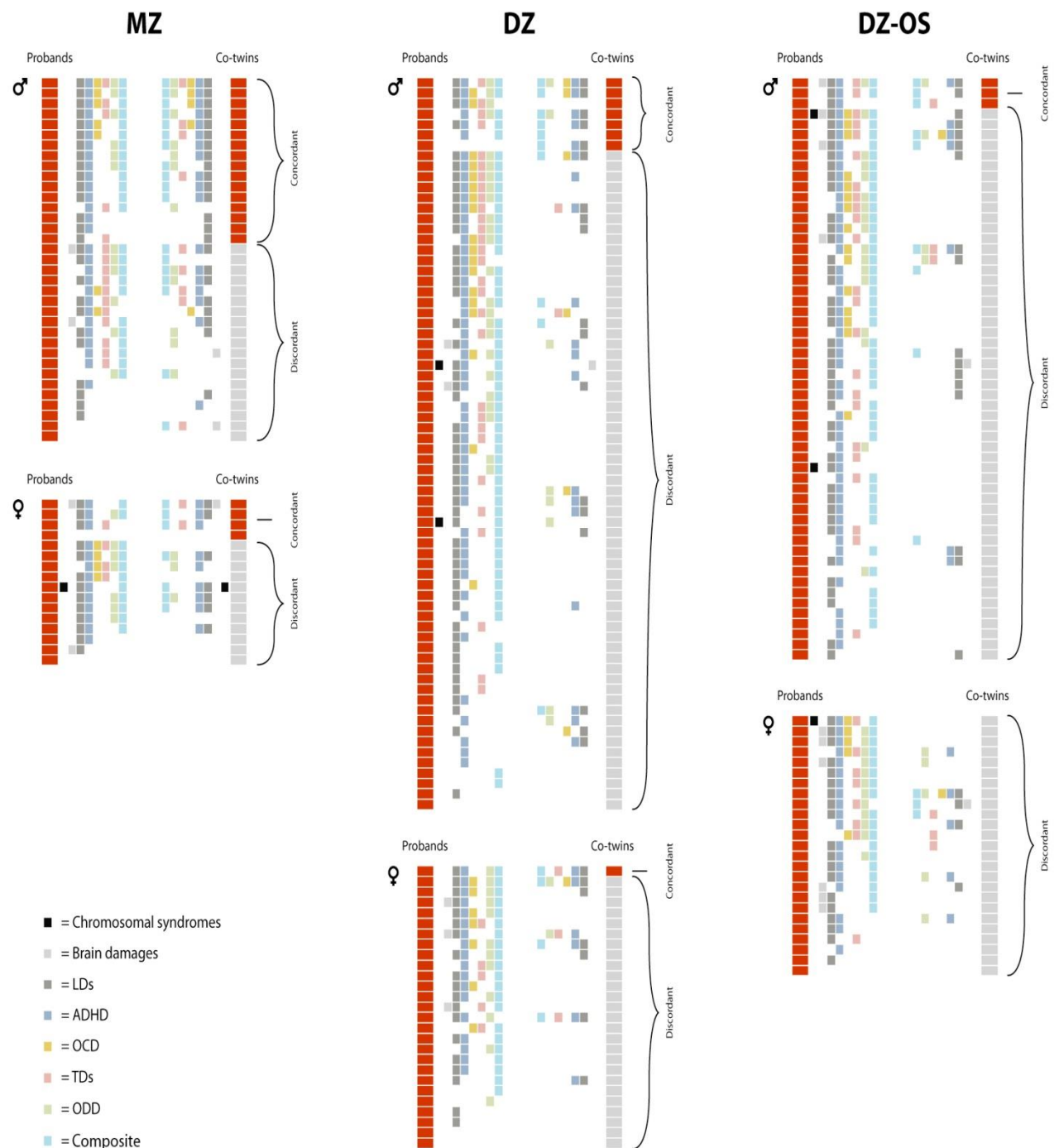


Figure 2. Coexisting disorders in twin pairs concordant or discordant for ASDs

Note: Each line in the categories (MZ, DZ, DZ -OS) represents a twin pair. Each square under the heading “Probands” or “Co-twins” represent an individual. Each square (to the right of “Probands” and left of “Co-twins”) represent coexisting disorders in that individual.

LDs= Learning Disabilities, ADHD=Attention Deficit Hyperactivity Disorder,
OCD=Obsessive compulsive Disorder, TDs= Tic Disorders, ODD = Oppositional Defiant
Disorder, Composite= developmental coordination disorder and/or executive dysfunctions
and/or perceptual problems

Supplementary material

Sources of ascertainment and overlap

A-TAC	Registers	Open question	Frequency
0	0	1	47
0	1	0	21
0	1	1	25
1	0	0	105
1	0	1	42
1	1	0	7
1	1	1	25

0 = no recorded ASD, 1= recorded ASD